of cognitive and affective impairment, as in patients not receiving radiotherapy. This theory, however, is not supported by the fact that the interval from diagnosis to testing in our study ranged from 1 year to more than 12 years without finding an influence of the length of the interval on neuropsychological function. This not only holds true for all patients studied, but also for the radiotherapy group.

Although we agree with Kreth and colleagues that a prospective clinical trial on this issue, with longitudinal cognitive and affective testing, is clearly to be preferred, this does not alter the fact that the main conclusion of our study remains well substantiated.

Department of Neurology
Free University Hospital
P.O. Box 7057
1007MB Amsterdam
The Netherlands

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Treatment of Guillain-Barré Syndrome with Intravenous Methylprednisolone

Richard Hughes, FRCP, and Anthony Swan, PhD

The Dutch Guillain-Barré Study Group [1] treated 25 patients with Guillain-Barré syndrome (GBS) with intravenous methylprednisolone (IVMP) and found that their functional improvement after 4 weeks was greater than that of 74 historical controls. We had previously published the results of a double-blind controlled trial of IVMP in 242 GBS patients [2] in which there was no difference in outcome between the patients treated with IVMP and those not so treated. The authors of the Dutch Study maintain that our trial was not conclusive, drawing attention to our own comments on the possible interference of plasma exchange (PE) with the outcome. In our trial the ethical imperative to permit the use of a procedure of proven and, at the time, unrivaled effectiveness, resulted in slightly more patients in the placebo group (77/118) than in the IVMP group receiving PE (66/124). In anticipation of this problem the randomizing neurologist was required to declare whether patients were to receive PE (63 placebo, 61 IVMP), not receive PE (27 placebo, 22 IVMP), or possibly receive PE (28 placebo, 41 IVMP). Allowing for age and sex differences, we studied the effects of IVMP in each of these groups separately and failed to detect either a significant beneficial or adverse effect in terms of grade change 4 weeks from randomization, or proportion improving by one or more grades after 4 weeks, or time to recovery of unaided walking.

Following publication of the Dutch trial of IVIG in GBS [3], a controlled trial of IVMP added to IVIG, as proposed by the Dutch Guillain-Barré Study Group [1], is now ethical and its interpretation will be less complicated. Like the Dutch investigators, we had also expected GBS to respond to steroids because the underlying pathological process is usually inflammatory and GBS forms part of a spectrum of conditions including chronic inflammatory demyelinating polyradiculoneuropathy, which does respond to steroids. Nevertheless, neither of the published controlled trials of steroids in GBS support their use [2, 4]. The provocative observations of the Dutch Guillain-Barré Study Group make a possible beneficial interaction between IVIG and IVMP worth exploring; but, until a more conclusive trial has been published, we do not recommend the use of steroids in GBS in practice.

Department of Neurology
UMDS, Guy's Hospital
London SE1 9RT, UK
PHLS Statistics Unit
61 Colindale Avenue
London NW9 5EQ, UK

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Reply

L. H. Visser and F. G. A. van der Meché

We thank Dr R. Hughes and Dr A. Swan for the additional information regarding their double-blind controlled trial of intravenous methylprednisolone (MP) in 242 patients with Guillain-Barré syndrome (GBS). Subgroup analysis did not reveal any significant beneficial effect of MP. Although we compared patients treated with MP with historical controls, we emphasize that both groups, the 25 patients of the pilot study as well as the 74 historical controls, were treated with intravenous immune globulins (IgIV) [1, 2]. We believe that available data support the conclusion that MP alone has little or no effect, but that MP in combination with IgIV (MP-IgIV) may give a synergistic response [1]. Actually, MP seems to have its effect during the first 2 weeks after start of therapy. Thirteen (52%) of the 25 patients treated with MP-IgIV showed an improvement in functional score in comparison with 20 (27%) of the 74 patients treated with IgIV (Table).

A multicenter double-blind study in which GBS patients are randomly assigned to either IgIV and placebo or to IgIV with MP has been designed and this trial started in August 1994. We fully agree with the recommendation of Drs

Effect of Treatment in Guillain-Barré Syndrome Patients During the First Two Weeks after Start of IgIV or MP-IgIV, Measured with a Seven-Point Functional Scale[a]

Difference in Functional Score in the First Two Weeks	IgIV (n = 74)	MP-IgIV (n = 25)
A Improvement	20 (27%)	13 (52%)
B Stable	37 (50%)	8 (32%)
C Deterioration	17 (23%)	4 (16%)

[a]Functional score: 0 denotes healthy; 1, having minor symptoms and signs but fully capable of manual word; 2, able to walk ≥10 m without assistance; 3, able to walk ≥10 m with a walker or support; 4, bedridden or chairbound; 5, requiring assisted ventilation for at least part of the day; and 6, dead.

IgIV = intravenous immune globulins; MP = methylprednisolone.

Hughes and Swan not to use steroids in GBS until the results of our pilot study have been confirmed by this double-blind trial.

Department of Neurology
University Hospital Rotterdam
40 Dr. Molewaterplein
3015 GD Rotterdam, the Netherlands

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Mechanism of Action of 4-Aminopyridine in the Symptomatic Treatment of Multiple Sclerosis

Floyd A. Davis, MD, Dusan Stefoski, MD, and Fred N. Quandt, PhD

4-Aminopyridine (4-AP) is believed to improve symptoms in multiple sclerosis (MS) by blocking internodal K channels and restoring conduction in blocked demyelinated axons. Like improvements in MS with body cooling, the effect is due to a prolongation of the action potential [1]. Recently, a letter submitted by Drs Felts and Smith [2] suggests that the action of 4-AP is at central synapses, to promote transmitter release, rather than at the site of demyelination. Although the letter was prompted by a report showing the lack of action of 3,4-diaminopyridine (3,4-DAP) in patients with demyelinating peripheral neuropathies [3], it has now been reported that higher doses of 3,4-DAP can reverse block in some of these conditions [4].

The main observation raised in their letter to support the alternative hypothesis is their finding that the minimum concentration of 4-AP required to reverse block in experimental demyelination is 100 μM, while the effective concentration of 4-AP estimated for effects in MS patients is much lower. The actual concentration in cerebrospinal fluid is difficult to estimate but may be higher than the value of 5 μM estimated by Felts and Smith [2].

However, it should be noted that the action of 4-AP to block K channels is now known to be at the cytoplasmic surface of the channel. 4-AP can block K channels recorded from a patch of membrane in an intact neuron when it is applied to the bath, but it must first cross the membrane to reach the 4-AP binding site [5, 6]. In addition, the sensitivity of K channels to 4-AP is much greater when applied directly to the cytoplasmic surface of the channel using inside-out patch clamped membranes than when applied to the external surface [5]. For 4-AP–sensitive K channels in mouse neuroblastoma cells, 25 μM 4-AP produces a greater effect when applied internally than does 500 μM 4-AP applied externally, a 20-fold difference in concentration [5]. Given these observations, it is probable that low concentrations of 4-AP outside accumulate inside a neuron over time and block at an internal site having high affinity. The effective concentrations in experiments in which 4-AP is applied over a short time may therefore not reflect the lower concentrations required in vivo. Accordingly, we feel that the hypothesis that 4-AP acts to promote conduction by block of axonal K channels cannot be ruled out by the argument cited by Felts and Smith [2]. The pharmacologic actions of 4-AP may well include an enhancement of transmitter release. However, the important issue is not whether the enhancement is more sensitive to 4-AP than block of axonal K channels. The question that needs to be resolved is whether an increase in synaptic activity can contribute to the mechanism by which 4-AP causes an improvement of signs in MS.

Multiple Sclerosis Center
Department of Neurological Sciences and Department of Physiology
Rush University
Chicago, IL 60612

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